

BUSINESS BRIEFS WEEK IN REVIEW

The feds cast a shadow over proton therapy as prospects brighten for the development of novel proton technology.

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They came to bury proton therapy, not to praise it
By Greg Freiherr

Initial clinical tests of a new PET biomarker, designed to determine the potency of malignant cancer cells in patients, indicate the feasibility of the biomarker as an in vivo agent. In development by Siemens and Fox Chase Cancer Center, the new agent is designed to capture and quantify the cellular expression of CA-IX, an enzyme linked to tumor growth and invasion, as well as hypoxia. Results of the so-called "phase 0" or "first-in-human" tests, conducted in healthy volunteers and presented Sept. 23 at the World Molecular Imaging Conference in Montreal, documented biodistribution of the new agent at safe levels for PET imaging and established it as stable 133 minutes after injection, a sufficient window for acquiring the image. The research also found that the agent safely clears the body in urine. Further clinical study is in progress, according to Siemens.

A heat-activated drug may boost the effectiveness of high-intensity focused ultrasound in its fight against difficult-to-treat cancers. The maker of the drug, Celsion, is working with Philips, the maker of the MR-guided HIFU system, to test the combination. Ultimately, the two companies

Engineers fiddle with new ways to stream protons

New ideas open door to high-energy cancer therapy, CT-like imaging

Proton therapy promises to reshape radiation oncology. Well-aimed beams of protons deposit more of their energy inside cancerous tissue and less in neighboring healthy tissue, say advocates of the approach. But the technology from which this promise has evolved is too big and too expensive to deliver much more than it already has.

The medical facilities where patient tumors are bombarded by protons—chunks of matter wrested from the nuclei of atoms—can cost between \$125 million and \$175 million to build. It's little wonder the U.S. has only about a half dozen such sites and that only about 25 are currently operating worldwide.

The clinical potential of proton therapy, however, has spurred efforts to come up with cheaper and much smaller ways to channel protons to cancer tumors inside patients. These include a "dielectric wall" at Lawrence Livermore National Laboratory (LLNL) in Berkeley, CA, and a high-power laser system at the University of Michigan.

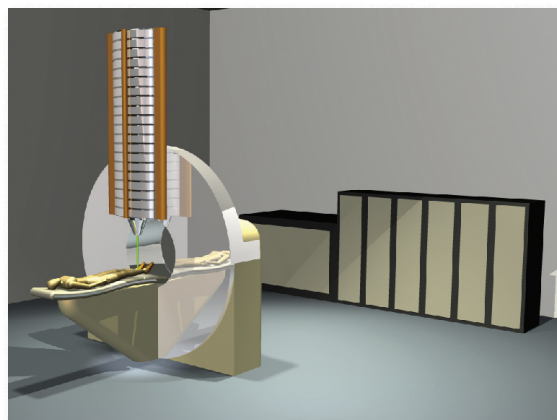
If either or both can produce sufficient protons to treat patients, it would be a snap to utilize their streams of protons to make images. In a twist on x-ray-based computed tomography, UCLA researchers propose proton CT (pCT). And

the increasing talk of proton therapy has given rise to the possibility of harnessing the proton's opposite: its four-times-more-powerful twin, the antiproton.

Meanwhile, the hubbub surrounding efforts to put protons to work in oncology has caught the ear of the Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ), which in mid-September attempted to dampen enthusiasm for proton therapy with a technical paper noting limited evidence for its clinical efficacy and safety. The agency put a positive spin on its findings of inadequate evidence, saying that "increased funding for comparative effectiveness research is an exciting opportunity to continue important research on medical therapies and interventions." But what made the agency pull the trigger on proton therapy was likely the chance that more proton centers might be coming soon, thanks to alternative and less expensive technologies for making proton streams (see commentary, "They came to bury proton therapy, not to praise it," page 4).

About 250,000 patients annually in the U.S. could benefit from proton therapy, according to ProCure, which is building proton therapy facilities based on the current and hyperexpensive technology. The half dozen or so proton centers currently operating can handle only about 3% of this estimated patient demand.

But George Caporaso, Ph.D., and colleagues at LLNL are developing a possible solution: a compact linear proton accelerator that uses high-gradient vacuum insulators and advanced dielectric



Artist's rendering of what a "dielectric wall" might look like if built into a proton therapy system. Alternative methods for generating protons, such as this one in development at the Lawrence Livermore National Laboratory, could dramatically cut the cost of facilities offering this form of cancer treatment.

hope to use the Philips system to target lesions with acoustic energy, creating sufficient heat to activate the pharmaceutical and preferentially release high concentrations of the chemotherapy drug doxorubicin to treat pancreatic cancer and cancer metastases in bone. With the feasibility stage now completed, preclinical development will focus on the combined use of Celsion's ThermoDox and Philips' MR-HIFU system.

Bruker BioSpin will build magnetic particle imaging (MPI) scanners for the preclinical market under an alliance struck by Bruker and Philips. Under the terms of the memorandum of understanding signed by the two companies, Bruker BioSpin intends to develop and manufacture pre-clinical MPI scanners at its facilities in Ettlingen, Germany. Both parties intend to comarket the resulting product. Developed by scientists at Philips, MPI produces 3D images of magnetic iron-oxide nanoparticles injected into the bloodstream, promising new information at organ, cellular, and molecular levels. The partnership combines Philips' strength in medical imaging and Bruker BioSpin's expertise in analytical MR instruments and preclinical MRI.

QUICK HITS:

High-resolution 3D/4D imaging distinguishes a new dedicated ob/gyn ultrasound system from competitors, according to its South Korean developer, **Medison**. The Accuvix V20 Prestige, which debuted last week at the International Society of Ultrasound in Obstetrics and Gynecology meeting in Hamburg, Germany, is optimized for evaluating pelvic and abdominal anatomy. It provides a 360° articulated monitor arm, ergonomic key grouping, and a 19-inch flat LCD screen with haze-eliminating filter.

GE Healthcare this week formally launched its hand-carried Venue 40 ultrasound product. The Venue 40 is designed for use at the patient bedside and during minimally invasive procedures. The company is framing the new product as the means for easily visualizing anatomy for biopsy guidance and line placement.

materials and switches to create medically usable protons. The goal of this "dielectric wall," according to Caporaso, beam research project leader at the laboratory, is to produce a proton accelerator as small as a standard linear accelerator, one that can deliver intensity-modulated proton therapy rather than x-ray therapy.

There's reason to believe such a development may be not too far away. A vendor of conventional radiation therapy, TomoTherapy of Madison, WI, has already licensed the new accelerator technology from LLNL. TomoTherapy is working with the laboratory and its partner, Compact Particle Acceleration, to develop a prototype accelerator for cancer therapy.

Dale Litzenberg, Ph.D., has a different idea. He is leading an effort at the University of Michigan to accelerate protons by bombarding a thin foil with light from a 300-terawatt laser. The electric fields within the short laser pulses cause a "coulomb explosion" in the foil that liberates protons. Litzenberg, a research assistant professor in the UM radiation oncology department, is working on a way to herd them into a beam for use in proton therapy.

Reinhard W. Schulte of the Loma Linda University Medical Center in Loma Linda, CA, would like to use proton beams, but not for therapy. Schulte is pioneering proton CT. By comparing the energy of each proton going in with its energy coming out, he thinks he can reconstruct an accurate map of the body's interior, one that includes tumors.

The technology is similar to that of current CT scanners, which digitally measure the attenuation of x-ray photons and reconstruct images based on these values. Energy loss from protons, however, may be much easier to detect, which means the dose of energy necessary to achieve the same image quality might be lower.

Computer studies done at Loma Linda University suggest that this pCT scanning would require from two to 10 times less dose to produce an image of resolution similar to that achieved with conventional CT. Submillimeter resolution can be attained for head-sized objects and millimeter resolution can be attained in other parts of the body, Schulte said. The pCT enterprise is still at an early stage of development and involves not only building the machines and detectors, but also developing advanced computer algorithms for extracting images from the measured data. But the work is promising, he said.

So is the flip side of the physics coin: using antiprotons for therapy. These antimatter counterparts of protons might deposit as much as four times more dose per particle than protons. The problem is making them. Antiprotons come from the collision of protons and a special target. For practical reasons, the advantages of antiprotons have yet to be verified through experience with actual tumors. Researchers guided by John DeMarco, Ph.D., chief of the clinical physics section in the UCLA radiation oncology department, are working out the logistics of antiproton therapy. They are building a treatment-planning system for this approach and studying the extraneous energy that might be deposited near the trajectory of an antiproton beam.

Drug-eluting stents prove safe, effective

Multicenter Asian trial focuses on patients with chronic total occlusions

Drug-eluting stents are effective and their use is associated with a low rate of acute complications, according to a multicenter study in Asia that examined patients with chronic total occlusions (CTOs) who were treated with percutaneous coronary intervention. Results of the study were reported Sept. 22 at the 21st annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium.

Researchers led by Dr. Sunao Nakamura, vice president and director of the cardiovascular center at New Tokyo Hospital, performed a prospective analysis of 1148 patients with about 1250 CTOs treated with different drug-eluting stents. Of these patients, 396 were treated with sirolimus-eluting stents (SES); 526 with paclitaxel-eluting stents (PES), 177 with zotarolimus-eluting stents (ZES), 66 with biolimus-eluting stents (BES), 41 with endothelial progenitor cell (EPC) capture stents (ECS), and 43 with everolimus-eluting stents (EES) in six high-volume Asian centers. The stents were applied after successful CTO recanalization at medical centers in Japan, the Republic of Korea, Indonesia, and Thailand.

Nakamura, who also serves as a clinical and visiting professor at Kumamoto University in Matsudo, Japan, reports that the incidence of major adverse cardiac events at 30 days was nearly nonexistent in patients with CTO lesions treated with drug-eluting stents. He singled out the BES and EES devices as being particularly safe and effective.

Major adverse cardiac events were recorded in only 0.4% of patients receiving PES, 0.6% in those receiving ZES, and 0% for all other types. At nine months, the incidence was 3.6% for those receiving SES, 6.7% for PES, 10.4% for ZES, 4.5% for BES, 10.3% for ECS, and 2.4% for EES. Target lesion revascularization at nine months was 3.6% for patients who received SES, 6.7% for PES, 10.4% for ZES, 4.5% for BES, 10.3% for ECS, and 2.4% for EES.

In addition, patients treated with SES, BES, and EES showed a lesser rate of angiographic restenosis at nine months compared with patients treated with other drug-eluting stents. The researchers found 4% restenosis for patients receiving SES, 6.7% for PES, 12.3% for ZES, 4.5% for BES, 10.3% for ECS, and 2.4% for EES.

Developers of novel PET radiotracer expand alliance

IBA and Aposense cut development and marketing collaboration

Aposense and Ion Beam Applications have agreed to share the cost of phase III clinical tests aimed at commercializing a PET radiotracer that promises to show—in a matter of days—whether a chemo regimen is helping cancer patients. The new agreement expands the two companies' collaboration, struck last year, to develop and supply the Aposense F-18-ML-10 radiotracer to multiple clinical trial sites in the U.S. and to develop the processes necessary for commercial-scale distribution.

Under this agreement, the two companies will share the cost of phase III trials of the radiotracer, which is designed to visualize apoptosis, a fundamental biological process of controlled cell death. They will also jointly market a commercial product if F-18-ML-10 meets regulatory approval in the various global markets for PET radiopharmaceuticals.

IBA and Aposense will share in development costs and subsequent revenues from the sale of a commercial product. IBA will focus primarily on its core PET imaging and nuclear medicine market. Aposense will concentrate its marketing efforts on referring clinical specialists. Specific financial terms have not been disclosed.

The experimental agent utilizes fluorine-18, the same PET isotope used in F-18 FDG. Because

apoptosis occurs in a wide range of medical disorders, molecular imaging with F-18-ML-10 could play an important role in the early detection of disease, as well as in indicating the course of the disease and assessing the effect of treatment or the development of novel therapies. In particular, F-18-ML-10 may assist oncologists in evaluating tumor response to treatment much earlier than conventional imaging modalities such as CT or MRI.

Such broad clinical value may be a while in coming, however. Phase II clinical trials of F-18-ML-10 under way at several U.S. cancer centers will not be done until next year. Phase III trials are expected to begin between 2011 and 2012. Data from these studies will be used as the basis for obtaining regulatory approvals. FDA reviews for new drugs typically take at least two years. If this is the case for Aposense F-18-ML-10, the radiotracer will not be commercially available until 2014 at the earliest.

Aposense and IBA are taking the long view. Their newly revised global agreement details the collaboration and joint funding of phase III trials and subsequent clinical development of F-18-ML-10. Aposense will manufacture the proprietary ML-10 precursor and IBA will label the agent with F-18 and distribute the final drug product to clinical sites through its global network of PET radiopharmacies.

IBA is a global supplier of PET radiopharmaceuticals. Company execs view the collaboration with Aposense as a means to expand IBA's position in this world market. To do that, IBA will leverage its network of PET radiopharmaceuticals production and distribution centers, one of the largest such networks in the world.

A kinder, gentler catheter debuts

Minor modifications promise less injury at contrast injection site

The force created when contrast media exit the end hole of a standard catheter may injure patients undergoing contrast-enhanced imaging studies. Cutting side holes and slits into the catheter may be the solution.

A study performed at Duke University Medical Center and scheduled to appear in next month's *American Journal of Roentgenology* compared

Toshiba America Medical Systems last week at the Transcatheter Cardiovascular Therapeutics meeting in San Francisco unveiled an advanced workstation for its Infinix-i systems, as well as a low-contrast capability for Infinix-i units featuring mid- and large-size flat-panel detectors. The Next Generation CV-3D workstation includes enhancements that optimize stent selection and positioning by automatically including markers and providing a view of the stent in relation to the vessel wall so as to assess stent deployment. The low-contrast capability delivers CT-like images of the liver, brain, and cerebral ventricles. LCI may be used to improve diagnosis, as well as to confirm appropriate endpoints during interventional procedures such as aortic stent-grafting, the company said.

Midwest Ultrasound, a provider of mobile ultrasound, has purchased 11 Xario XG ultrasound systems from **Toshiba America Medical Systems** as part of a two-year purchase agreement. The systems will be utilized at various rural and community hospitals, including The Christ Hospital in Cincinnati. Midwest Ultrasound, a wholly owned subsidiary of The Christ Hospital, plans to purchase additional systems for use at other clients' facilities during the course of the partnership.

Agfa HealthCare will resell two products developed by peerVue as integral parts of its Impax 6.0 PACS. One is a workflow, quality, and communication product called qiVue. The other is a teaching file and content management product called caseVue. By allowing critical results reporting, peer review, emergency department discrepancy management, and technologist quality control, as well as the generation of teaching files, Agfa says the newly integrated products will enable radiology departments to meet requirements for accreditation by the American College of Radiology.

Barco has signed Fineman GmbH to resell its medical displays in Germany. Fineman A/S, the parent company of the newly signed Ratingen, Germany-based distributor, has been selling Barco products in Denmark for several years.

Gamma Medica-Ideas has raised \$24 million to support efforts to grow its presence in the clinical marketplace with digital SPECT, PET, and CT products. **Psilos Group**, a healthcare venture capital firm, and **Capital Resource Partners**, a provider of hybrid growth financing, contributed \$14 million in equity capital. Capital Resource Partners also provided \$5 million in mezzanine debt. The technology lending group at Bridge Bank rounded out the financing with a \$5 million revolving line of credit.

Revenues decreased 17% for **InSight Health** in the fourth quarter, adding to an already down year for the provider of outpatient and mobile imaging services. For fiscal 2009, ended June 30, revenues decreased 13% from approximately \$265 million in the previous fiscal year. In the fourth quarter, revenues from fixed operations decreased approximately 21% to \$32.3 million, principally due to declines at imaging centers. Revenues from mobile operations decreased approximately 12% to \$21.3 million, primarily due to reductions in reimbursement from its customers and a decline in the number of customers served. For the fiscal year, revenues for fixed operations decreased approximately 17.5% to \$139 million, while those for mobile operations decreased 6% to \$90 million.

PEOPLE:

David Fisher will lead the Medical Imaging and Technology Alliance, a division of the National Electrical Manufacturers Association representing the makers of medical imaging equipment. Currently the senior health policy advisor for the Senate Budget Committee, Fisher has held senior level jobs over 12 years in the federal government, including in both houses of Congress. Recently he served as associate director of the Office of Management and Budget, where he oversaw the departments of Health and Human Services and Education and Labor, the Social Security Administration, Railroad Retirement Board, and a number of programs administered by the U.S. Department of Agriculture.

fluid flow from such modified catheters and from standard ones. The addition of side holes or slits cut the velocity of contrast material exiting the end hole of the catheter by 9% to 30%, according to the research.

"We saw more of a cloud-like dispersal rather than a jet," said Dr. Rendon C. Nelson, senior author of the study and a Duke professor of radiology.

The problems addressed by this solution are relatively rare and non-life-threatening, he said. They do, however, crop up regularly. At the Duke University Medical Center, about 14 or 15 patients per month suffer injuries that can be traced back to the flow of contrast media during IV infusion, Nelson said. Typically the injuries are mild, such as pain and swelling at the injection site.

But they can be more severe, Nelson said. He noted that with only a slight modification, the problem might be prevented.

COMMENTARY



They came to bury proton therapy, not to praise it

BY GREG FREIHERR

Using logic that could just as easily be applied when considering a toddler, the federal

government damned proton therapy on Sept. 14 with a report that brands the cancer treatment as lacking evidence of effectiveness and safety.

"Particle beam radiation therapy can target the radiation with a high degree of precision, but its potential advantages over other radiotherapy alternatives have not been verified in long-term outcome studies," according to a technical brief from the Department of Health and Human Services' Agency for Healthcare Research and Quality (AHRQ).

Some clinicians consider proton therapy to be better than traditional cancer radiation treatments, the agency said in its brief, "but there is limited evidence about its safety compared with other types of radiation therapy."

This should come as no surprise, particularly to AHRQ. The agency notes that there are only seven centers in the U.S. at which proton therapy is available.

The advocates of proton therapy are ambitious, however, and that ambition may have something to do with the report's appearance now. A

company called ProCure has plans to build more such centers; one is expected to open next year. And the AHRQ report states that several other hospitals are considering developing smaller treatment facilities "based on technologies that have not yet been cleared by the Food and Drug Administration."

Rather than greet these developments with enthusiasm, the agency seemed determined in its brief to put as negative a slant as possible on what is known about proton therapy. The technical brief specifically stated that there is no indication that this type of radiation therapy is riskier than conventional radiation therapy, but then said "most studies were conducted on small numbers of patients and did not compare the safety of particle beam radiation therapy against other therapies."

In short, the technical brief concludes that there's really not much to say about proton therapy. Why then publish such a report? The reason, according to the agency, is to "highlight where more research is needed and where research may be sufficient to warrant a full systematic review."

If one goal is to highlight where more research is needed, wouldn't it have made more sense to send the report findings specifically to the handful of centers providing proton therapy? Similarly, if identifying where research may be sufficient to warrant a full systematic review is the other goal, wouldn't that be an internal matter better suited to an intra-agency memo? In fact, AHRQ is currently reviewing scientific studies on radiation therapies for head and neck cancers and proton therapy made the cut. The agency will evaluate its clinical effectiveness in this context. So, if this purpose is already satisfied, again, why publish the report?

I can think of no more effective way to keep a lid on a medical technology than to discourage investment early in its development. How better to do this than to come out with a report that labels the therapy as unproven and notes that hospitals are considering the use of technologies that have not been cleared by regulators.

Rather than meeting its stated goals of promoting knowledge about proton therapy, the AHRQ seems to have launched a thinly veiled attack on this form of cancer therapy, one that fits an evolving pattern within the DHHS. Time and again this department, acting through one or another of its agencies, has taken whacks at high technology.

This pattern of attack will intensify as long as technology bears the blame for spiraling healthcare costs. Inefficiency is the real culprit. Flogging technological scapegoats is doomed to fail, as it allows the real problems to persist. But bureaucrats responsible for healthcare in this country can't seem to grasp that.